



Simplified models of neocortical pyramidal cells preserving somatodendritic voltage attenuation

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Abstract

Simplified models are needed for performing large-scale network simulations involving thousands of cells. Ideally, these models should be as simple as possible, but still capture important electrotonic properties, such as voltage attenuation. Here, we propose a method to design simplified models with correct voltage attenuation, based on camera-lucida reconstructions of neurons. The simplified model geometry is fit to the detailed model such that it preserves: (i) total membrane area, (ii) input resistance, (iii) time constant and (iv) voltage attenuation for current injection in the soma. Using the three dimensional reconstruction of a layer VI pyramidal cell, we show that this procedure leads to an efficient simplified model which preserves voltage attenuation for somatic current injection as well as for distributed synaptic inputs in dendrites. Attenuation was also correctly captured in the presence of synaptic background activity. These simplified models should be useful for performing network simulations of neurons with electrotonic properties consistent with detailed morphologies. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Simplified models are needed for performing large-scale network simulations, because of the considerable computation requirement and complexity of

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morphologically-realistic models. Systematic approaches for designing simplified models with electrical behavior equivalent to more detailed representations started with the concept of “equivalent cylinder” introduced by Rall [11,12]. The equivalent cylinder representation of a neuron is however only possible under specific morphological constraints: all dendrites must end at the same electrotonic distance to soma and branch points must follow the 2/3 power rule, which makes it applicable only to a small subset of cellular morphologies.

Another approach was proposed more recently [13] consisting of drawing a “cartoon” model in which the pyramidal cell morphology was reduced to 24 compartments. A related approach was also proposed to design simplified models based on the conservation of axial resistance [1]. The latter type of reduced model had the same total axial resistance as the original model, but the membrane area was not conserved. A rescaling factor had to be applied to capacitance and conductances, to compensate for the different membrane area and yield correct input resistance.

We introduce here a method for obtaining reduced models that preserve membrane area and voltage attenuation with as few as 3 compartments. Complex morphologies are collapsed into equivalent compartments to yield the same total membrane area. The axial resistances of the simplified model are adjusted by fitting, such that passive responses and voltage attenuation are identical between simplified and detailed models. The reduced model thus has the same membrane area, input resistance, time constant and voltage attenuation as the detailed model. We illustrate how well it accounts for other situations such as the attenuation of synaptic potentials and the electrotonic structure in the presence of synaptic background activity.

2. Results

To reduce the complexity of detailed models, the first step is to identify different functional regions in the dendritic morphology. A possibility is to choose these regions based on morphology and/or the distribution of synapses in the cell. For example, in neocortical pyramidal cells, these regions can be (a) the soma and the first 40 μm of dendrites, which are devoid of spines [6,9] and mostly form inhibitory synapses [7]; (b) all dendrites laying between 40 μm and about 240 μm from the soma, which includes the vast majority of basal dendrites and the proximal trunk of apical dendrite; (c) all dendrites laying farther from 240 μm from the soma, which contains the major part of the apical dendritic tree. The latter two regions (b and c) contain nearly all excitatory synapses [3,15]; they also contain inhibitory synapses although at lower density than in the soma. Thus, in the case of pyramidal cells, these considerations lead to three different functional regions that can be used to build a reduced model.

The second step is to identify each functional region with a single compartment in the reduced model and calculate its length and diameter. To allow comparison between the models, the length of the equivalent compartment was chosen as the typical physical length of its associated functional region, and the diameter of the equivalent compartment was chosen such that the total membrane area is the same as

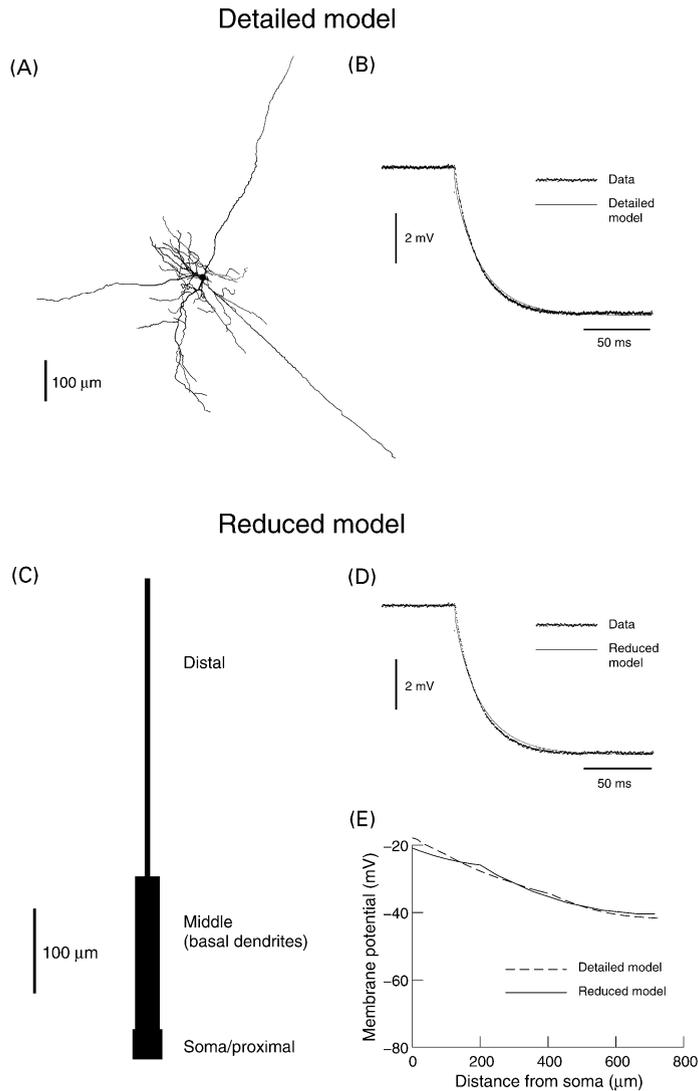


Fig. 1. Simplified 3-compartment model of layer VI neocortical pyramidal cell. (A) Dendritic morphology of a layer VI pyramidal cell from cat parietal cortex (from Ref. [2]). (B) Best fit of the model to passive responses obtained experimentally ($g_{\text{leak}} = 0.045 \text{ mS cm}^{-2}$, $C_m = 1 \text{ } \mu\text{F/cm}^2$ and $R_i = 250 \text{ } \Omega\text{cm}$; see Ref. [4]). (C) Simplified 3-compartment model obtained from the layer VI morphology in A. The length and area of each compartment were calculated based on length and total area of the parent dendritic segments (see text). (D) Adjustment of the 3-compartment model to passive responses (same experimental data as in B). (E) Adjustment of the 3-compartment model (continuous line) to the profile of voltage attenuation at steady state in the original layer VI model (dashed line; horizontal dashed line indicates the resting membrane potential; each curve is an average over 10 s of activity with 0.8 nA injection in soma). Axial resistivities were adjusted by the fitting procedure, which was constrained by D and E simultaneously.

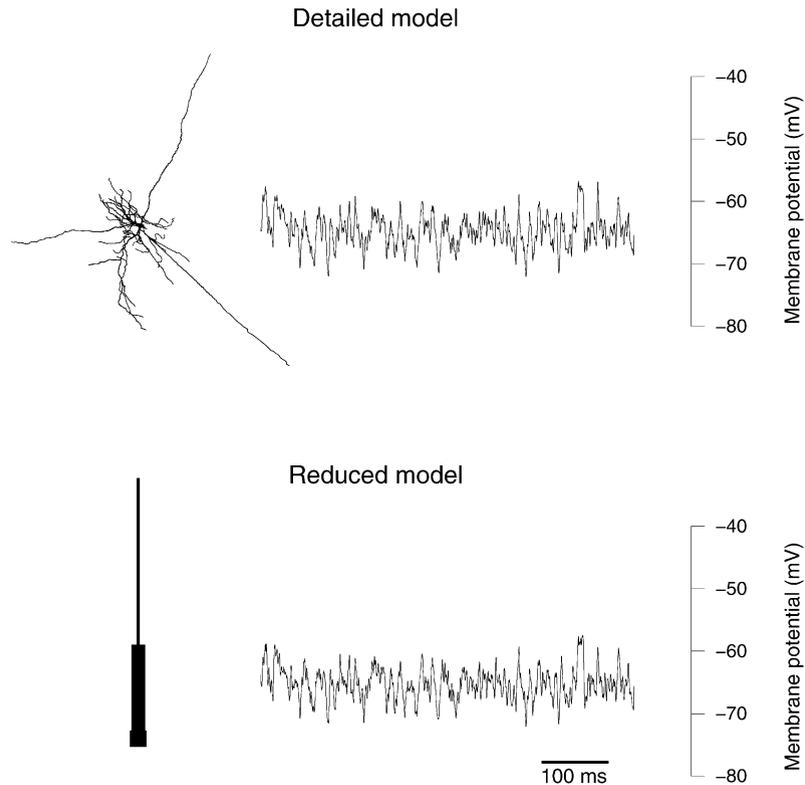


Fig. 2. Simulation of synaptic background activity. A. Synaptic background activity in the Layer VI pyramidal neuron described in Fig. 1A. A large number of randomly occurring synaptic inputs (16563 glutamatergic and 3376 GABAergic synapses) were simulated in all compartments of the model (see details in Ref. [4]). B. Same simulation using the same number of synaptic inputs in the reduced model. Both models gave membrane potential fluctuations of comparable fine structure.

the ensemble of dendritic segments it represents. For example, in the layer VI pyramidal cell considered here (Fig. 1A), we identified three compartments: the soma and first 40 μm of dendrites (“soma/proximal” compartment), the dendritic region between 40 and 240 μm (“middle” compartment), containing the majority of basal dendritic branches, and the dendritic segments from 240 to about 800 μm (“distal” compartment), which includes the apical dendrites and the distal ends of the longest basal branches. The lengths and diameters were: $L = \text{diam} = 34.8 \mu\text{m}$ (soma/proximal), $L = 200 \mu\text{m}$ and $\text{diam} = 28.8 \mu\text{m}$ (middle), $L = 515 \mu\text{m}$ and $\text{diam} = 6.20 \mu\text{m}$ (distal), yielding a reduced model with the same total membrane area as the detailed model (Fig. 1C).

The third step is to provide the reduced model with correct passive properties and voltage attenuation. To this end, the same passive parameters as the detailed model were used, except for the axial resistivities which were adjusted by a multiple fitting

procedure [10] constrained by passive responses (Fig. 1D) and somatodendritic profile following current injection (Fig. 1E). The optimal values were $4721 \Omega \text{cm}$ (soma/proximal), $3560 \Omega \text{cm}$ (Middle) and $896 \Omega \text{cm}$ (distal). These values are high compared to recent estimates [14] because each equivalent compartment represents here a large number of dendritic branches that were collapsed together. Thus in these conditions, the reduced model has a total membrane area, input resistance, time constant and voltage attenuation consistent with the detailed model.

To test the performance of this model, we first simulated synaptic background activity, in which a large number of randomly occurring synaptic inputs were distributed in all compartments of the model (Fig. 2). Synaptic currents were modeled by kinetic models of glutamatergic and GABAergic receptors [5] which distribution was based on morphological studies in pyramidal neurons [3,15] (see details in Ref. [4]). Simulated background activity consisted of a total of 16563 glutamatergic and 3376 GABAergic synapses distributed in dendrites and releasing randomly according to Poisson processes (Fig. 2, Detailed model). Remarkably, simulating the same number of synapses in corresponding locations in the reduced model led to membrane potential fluctuations of similar fine structure at the soma (Fig. 2, Reduced model).

We next considered the variations of input resistance (R_{in}) and average somatic membrane potential ($\langle V \rangle$) due to the presence of synaptic background activity. In the layer VI pyramidal cell model, the R_{in} and $\langle V \rangle$ varied as a function of the release frequency at synaptic terminals (Fig. 3A, symbols; see details of this model in Ref. [4]). The reduced model behaved remarkably similarly to the layer VI model when the same densities of synaptic conductances were used (Fig. 3A, continuous lines). This was not possible using a single-compartment model (not shown).

Two additional properties were correctly captured by the reduced model compared to the layer VI model. First, the profile of voltage attenuation in the presence of background activity was similar in both models (Fig. 3B). The simplified model thus reproduces the observation that background activity is responsible for a ~ 5 -fold increase in voltage attenuation [4] (compare Fig. 3B with Fig. 1E). Second, stimulation of synaptic inputs distributed in distal dendrites also gave similar EPSPs amplitudes in soma in both models, in the presence of background activity (Fig. 3C, Active) and in quiescent conditions (Fig. 3C, Quiescent).

3. Discussion

In conclusion, we suggest a procedure to obtain simplified models by fitting the axial resistances constrained by passive responses and voltage attenuation. The model obtained preserves the membrane area, input resistance, time constant and voltage attenuation of more detailed morphological representations. It also captures the electrotonic properties of the neurons in the presence of synaptic background activity. This model was one to two orders of magnitude faster to simulate.

However, this model does not account for the attenuation of isolated dendritic events (not shown), because the current flowing in the individual dendritic branches

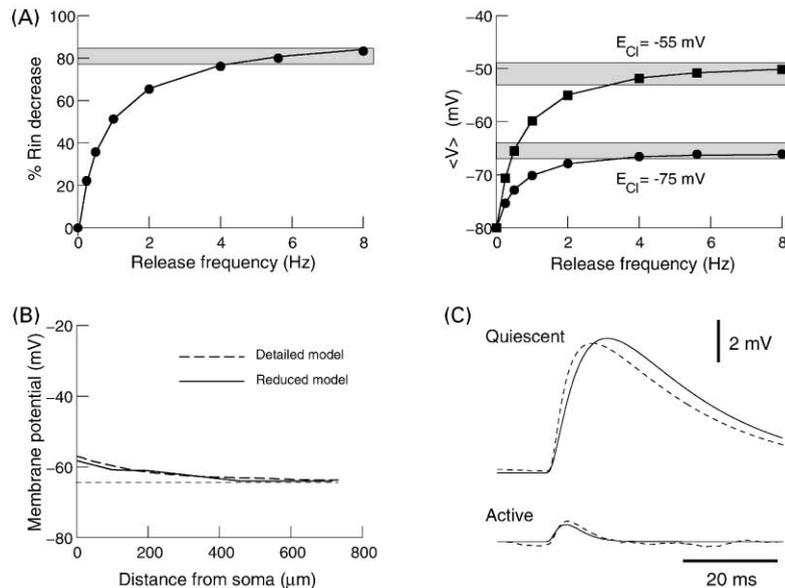


Fig. 3. Behavior of the 3-compartment model in the presence of synaptic background activity. (A) Decrease in input resistance (R_{in}) and average membrane potential ($\langle V \rangle$) in the presence of synaptic background activity (E_{Cl} is the chloride reversal potential). The behavior of the 3-compartment model (continuous line) was remarkably similar to that of the layer VI pyramidal cell model (symbols; data from Ref. [4]). The values measured intracellularly in cat parietal cortex in vivo [4,8] are shown in gray for comparison. (B) Voltage attenuation in the presence of synaptic background activity. The 3-compartment model (continuous curve) is compared to the layer VI pyramidal cell model (dashed line; 0.8 nA injection in soma) in the presence of background activity (same scale as in Fig. 1E). (C) Attenuation of distal EPSPs. A 100 nS AMPA-mediated EPSP was simulated in the distal dendrite of the simplified model (continuous traces) and is compared to synchronized stimulation of the same synaptic conductance distributed in distal dendrites of the layer VI pyramidal cell model (dashed lines). The EPSP was of 5.6 mV amplitude without background activity (Quiescent) and dropped to 0.68 mV in the presence of background activity (active). Both models generated EPSPs of similar amplitude.

must be taken into account in this case. Modeling this type of events would require taking into account the details of the dendritic structure. The reduced models presented here are however well suited for paradigms in which synaptic inputs are distributed in dendrites, such as typically during background activity. It should also be useful to obtain accurate simplified representations of neurons containing particular somatodendritic densities of voltage-dependent currents.

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